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(57) Abstract

The present invention relates to the use of non–steroidal antiinflammatory compounds for the prevention and the treatment of neurodegenerative diseases such as Alzheimer' and Parkinson's disease.

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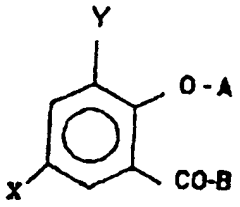
USE OF SELECTED NON-STEROIDAL ANTIINFLAMMATORY COMPOUNDS FOR THE PREVENTION AND THE TREATMENT OF NEURODEGENERATIVE DISEASES

The present invention relates to the use of selected non-steroidal antinflammatory compounds for the prevention and the treatment of glutamate receptor-mediated neuronal damages, such compounds being selected from:

(a) the group of compounds deriving from acetylsalicylic acid of the following formula (I)



(I)

wherein:

A is H; (C_1-C_4)-alkyl, optionally substituted with a carboxyl group; (C_3-C_4)-alkenyl or alkynyl; phenyl optionally substituted with a carboxyl group; naphthyl; COR, SO_3R;

B is OR^1; NHR^2;

R is (C_1-C_4)-alkyl;

R^1 is H; an ammonium cation; a pharmaceutically acceptable cation of an alkali or alkaline-earth metal or of an organic base; (C_1C_4)-alkyl, optionally substituted with a hydroxyl or phenoxyl group, which can in its turn optionally be substituted with an acetamino group; phenoxyl optionally substituted with an acetamino group;

R2 is H; (C_2-C_4)-alkanoyl;

X is OH; NH_2; phenyl optionally substituted with one or more fluorine atoms; 4,5dihydro-2-phenyl-3H-benzindol-3-yl; p-aminobenzenesulfonamido; 4-[(pyridinylamino)sulfonyl]phenyl-;

Y is H; OH;

and the pharmaceutically acceptable salts and metabolites thereof;

(b) the group of compounds with antiinflammatory activity consisting of tolmetin, ketorolac, diclofenac, ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, piroxicam, tenoxicam, nabumetone, aminopyrine, apazone, phenylbutazone, oxyphenbutazone, antipyrine, nimesulide, sulindac, etodolac, mefenamic acid, sodium meclofenamate, zileuton;

and the pharmaceutically acceptable salts and metabolites thereof;

(c) benzoic acid, 2,3-dihydroxy-benzoic acid and sulfanylamide;

and the pharmaceutically acceptable salts and metabolites thereof;

for the preparation of a medicament for the prevention and/or the treatment of glutamate receptor-mediated neuronal damages.

Examples of cations deriving from pharmaceutically acceptable organic bases are aliphatic organic amines, such as glucamine, cyclic amines, such as morpholine, heterocyclic amines such as imidazole, and those deriving from amino acids, such as lysine.

The compounds of general formula (I) comprise medicaments having antiinflammatory and/or analgesic and/or antipyretic activities (NSAID) selected from the

group consisting of acetylsalicylic acid (ASA), sodium salicylate (NaSal), salicylamide, salicylamide- Oacetic acid, salacetamide, flufenisal, diflunisal, acetaminosalol, calcium acetylsalicylate, benorylate, fendosal, salicyl-sulforic acid, etersalate, gentisic acid, glycol salicylate, mesalamine, imidazole salicylate, lysine acetylsalicylate, morpholine salicylate, 1-naphthyl salicylate, parsalmide, phenyl acetylsalicylate, salsalate, sulfasalazine, olsalazine, methyl salicylate, methyl acetylsalicylate.

A preferred embodiment of the present invention provides the use of ASA or of its metabolite, NaSal, for the prevention and/or the treatment of glutamate receptor-mediated neuronal damages.

ASA is undoubtedly the most widely employed medicament among NSAIDs, thanks to it its very wide pharmacological spectrum which makes ASA suitable, at different dosages, as an analgesic, antinflammatory and antipyretic agent and for limiting the risk of cardiac diseases as well as episodic ischemic syndromes; recently the lower incidence of lung, colon and breast cancer following the repeated administration of ASA has been proved.

The hypothesis that inflammatory processes contribute to the pathology of neurodegenerative diseases, particularly Alzheimer' disease (AD), is supported by clinical and epidemiological studies [P.L. McGeer et al., Lancet 335, 1037 (1990); P.L. McGeer et al., Neurology 42, 447 (1992); J.C.S. Breitner et al., Neurology 44, 227, (1994); J.C.S. Breitner et al., Neurobiol. Aging 16, 523 (1995); J.B. Rich et al;

Neurology 45, 51 (1995); K. Andersen et al., Neurology 45, 1441 (1995)] which indicated that patients administered with antinflammatory medicaments or who were affected by other pathologies for which said medicaments are usually employed, show a lower risk of developing AD.

Moreover, it has been proved [J. Rogers et al. Neurology 43, 1609, (1993)] that another NSAID reduces the progression of cognitive decline in AD patients.

Despite their wide use in several clinical settings, the mechanism underlying the pharmacological properties of non-steroidal antinflammatory drugs has not been completely established. Drug effectiveness has been ascribed to the ability to prevent prostaglandins (PGs) and thromboxanes (TXs) production by inhibiting the enzyme cyclooxygenase (COX) [P. Insel, in Goodman and Gilman's The pharmacological Basis of Therapeutics (McGraw-Hill, New York, 9th ed. pp. 617-657; G. Weismann, Sci. Am., 264, 84 (1991); K.D. Rainsford, in Acetylsalicylic acid and the Salicylates (Butterworths, London, 1984); J.P. Famaey et al., Therapeutic Applications of NSAIDs Subpopulations and New Formulations (Dekker, New York, 1992)].

Nevertheless, some inconsistencies within this hypothesis make the mechanism of action of these drugs still a matter of debate. For instance, salycilic acid lacks inhibitory activity on COX. Moreover, doses of drugs needed to treat chronic inflammatory diseases are consistently higher than those required to inhibit PGs synthesis.

Now it has surprisingly been found, and it is an object of the present invention, that the above non-

steroidal antinflammatory compounds of formula (I) and the pharmaceutically acceptable salts and metabolites thereof have properties making them suitable for the prevention and/or the treatment of glutamate receptor-mediated neuronal damages, independently of any antiinflammatory properties thereof, at concentrations compatible with the plasma levels kept during the treatment of an inflammatory condition such as arthritis.

In fact, said compounds unexpectedly and independently of any antiinflammatory properties thereof show a protective activity against glutamate-induced neurotoxicity.

Glutamate is the most abundant excitatory neurotransmitter in the brain. However, under certain undefined conditions, it may become a potent excitotoxin. Its contribution to the neurodegeneration associated with several acute and chronic neurodegenerative disorders, including AD, is widely established [Lipton et al,, New Engl. J. Med. 330, 613-622 (1995); M. Memo et al., Int. Rev. Psych. 7, 339 (1995)].

Several models of neurons in culture have been extensively used to unravel the molecular events triggered by glutamate and leading to cell death as well as to develop a variety of pharmacological compounds able to counteract excitotoxicity. Among them, the primary culture of rat cerebellar granule cells has been selected, where a brief pulse of glutamate, through activation of the glutamate receptor belonging to the N-methyl-D-aspartate (NMDA) subtype, induces cell death [Gallo et al., Proc. Natl. Acad. Sci. USA 79, 7919-7923; M. Favaron et al., Proc. Natl. Acad. Sci. USA 85, 7351

(1988)].

Particularly preferred is the use of acetylsalicylic acid (ASA) and/or of its metabolite, sodium salicylate (NaSal).

Also preferred are salicylic acid, salicylamide, salicylamide-O-acetic acid and salacetamide and those ASA and NaSal derivatives having bioavailability characteristics at the brain level.

It has been found that such non-steroidal antiinflammatory compounds are particularly suitable for use in the prevention of glutamate receptor-mediated neuronal damages related to Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, Parkinson' disease, cranial and spinal traumas, multi-infarct dementia, Lewy Body dementia, AIDS-associated dementia, central and peripheral ischemic neuropathies, neuropathies due to anoxic and/or glycemic damages, multiple sclerosis, infective and/or toxic neurodegenerative diseases, neurodegenerative syndromes in prion diseases, ataxias-telangiectasias, epilepsy-related neurodegenerative processes, metabolic neuropathies and other related neuropathologies.

A further object of the present invention is the use of non-steroidal antiinflammatory compounds for the preparation of a medicament for the prevention and/or the treatment of glutamate receptor-mediated neuronal damages.

In order to prove the protective activity of compounds with formula (I) against glutamate neurotoxicity, ASA and NaSal were added to the culture medium 5 min before the addition of glutamate. Glutamate

was used at a 50 μM concentration, which concentration is capable of reducing cell survival by 70-80 %.

The range of the concentrations used for both drugs is related, as it is shown in the following table, to the plasma levels reached during the antiinflammatory therapy of patients affected with rheumatic diseases.

Table

Relationship between plasma levels maintained during antiinflammatory therapy of humans, neuroprotective effect of the tested compounds and COX inhibition.

Agent	Plasma levels	Tested doses	Hippocampus neuroprotection (EC_{50})	Primary neurons neuroprotection (EC_{50})	COX inhibition
ASA	1-3 mM	1-3 mM	< 3 mM	1.7 mM	+
NaSal	1-3 mM	2-10 mM	< 2 mM	5 mM	-
indomethacin	1-20 µM	1-20 µM	ND	NS	+
NaCl		20 mM	ND	NS	

ND: not determinated NS: not sufficient

As shown in Fig. 1, a dose-dependent protection against glutamate-induced neurotoxicity was observed in the presence of both drugs. For ASA, the calculated value, i.e. the mean effective concentration inducing a 50% effective response (hereinafter referred to as EC_{50}) was 1.7 mM, with a maximum effect (equivalent to 83% protection) exerted at 3 mM. The concentration of NaSal giving 50% of protection was about 5 mM, with a maximal response (87% protection) observed at 10 mM.

Unlike salicylates, indomethacin was unable to prevent glutamate-evoked cell death at doses compatible with the plasma levels during drug chronic treatment, (1-20 mM) (Table 1).

Neuroprotection was also evaluated in a different experimental model corresponding to slices of 8 day-old rat hippocampus. This experimental setting offered several advantages compared to primary cultures of neurons, which make it more predictive for an in vivo effect of these drugs. First of all, hippocampus contains the neurons which are the most vulnerable to excitotoxic damage, namely the granular and pyramidal; additionally, the ex vivo preparation represents an heterogeneous population of neurons which have been differentiated in vivo.

In agreement with previous findings, stimulation of the NMDA receptor subtype by application of the selective agonist (NMDA, 30 µM, for 30 min) specifically induced a characteristic cell injury.

Most pyramidal neurons of CA1, CA3 and granule cells of dentate gyrus (DG) exposed to NMDA became acutely necrotic: they exhibited highly swollen cytoplasm

containing large vacuoles, nuclear shrinkage and focal clumping of chromatin.

It has been found that the application of ASA preserved hippocampal cell viability from the NMDA-mediated injury.

The effect of ASA was evaluated at concentrations ranging from 1 to 10 mM. A quantitative analysis of the results is summarized in Fig. 2. In this experimental model ASA did not modify cell viability at 1 mM concentration, while at 3 mM it specifically produced a significant neuroprotection in the CA3 region. Higher concentrations of ASA elicited an almost complete prevention of NMDA effect even in CA1 and DG, besides CA3.

The drug did not modify per se neuron viability.

Interestingly, NaSal already at 2 mM concentrations was capable of efficiently counteracting NMDA-mediated toxicity in hippocampal slices (Fig. 2) compared to what observed in primary cultures of rat cerebellar granule cells.

In the attempt to dissect the molecular mechanisms by which salicylates protect cell viability against glutamate-induced neurotoxicity, the possibility that these drugs might counteract glutamate-evoked cell death by diminishing the NMDA-mediated calcium entry was investigated.[D.W. Choi, J. Neurosci. 7, 369 (1987). The hypothesis was tested in primary cultures of rat granule cells by measuring the intracellular calcium concentration by means of microfluorimetry. Application of glutamate in the absence of external Mg^{2+} caused a rapid increase in calcium concentration followed by a

sustained plateau (Fig. 3), mainly due to the NMDA receptor subtype activation.

Cytosolic free calcium concentration was investigated in single cells by microfluorimetric technique using the fluorescent probe "Fura 2" (from Sigma) as described by M. Pizzi et al. in Mol. Pharmacol. 49, 586 (1996). Cells were exposed to glutamate for 2 min in the chamber containing Mg^{2+}-free Krebs-Ringer solution (KRS). ASA and/or NaSal were added to the chamber 2 min before glutamate exposure. Fluorescence image acquisition and analysis were performed by MIRAcal (Multiple Image Rationing and Analysis with Calibration) system by Applied Imaging (UK).

ASA, applied at neuroprotective concentrations ranging from 1 to 3 mM, induced no changes in cell responsiveness to glutamate. It should be noted that the drug induced per se an exceedingly limited and transient increase in calcium concentration.

A representative experiment performed utilizing 3 mM ASA is depicted in Fig. 3B.

Similarly, NaSal at neuroprotective concentrations ranging from 2 to 10 mM, did not modify cell responsiveness to glutamate, although inducing per se a limited, transient increase in calcium concentration.

These results strongly excluded a possible negative modulatory effect of both ASA and NaSal on the NMDA receptor efficiency and suggested their interference with intracellular molecular targets further downstream glutamate receptor activation in the cascade of events triggering excitotoxicity. To this regard, salicylates appear distinguishable from most drugs endowed with

neuroprotective properties. Moreover, these data indicate that neuroprotection can occur independently of the mechanisms controlling calcium concentration homoeostasis.

Administration of glutamate to primary cultures of rat cerebellar granule cells also results in upregulation of the NF-kB nuclear activity and of the transcriptional complex AP-1 (Fig.4). Cells were exposed to 50 μM glutamate in the absence or presence of ASA (1, 3 mM) and NaSal (3, 10 mM) and nuclear extracts were prepared 1 h after stimulation. Nuclear extracts from rat cerebellar granule cells were subjected to an electrophoretic mobility-shift assay with γ-^{32}P-labeled oligonucleotide probes containing the immunoglobulin kB (lanes 1 to 6) and the AP-1 DNA binding sites (lanes 7 to 12). Cells were either unstimulated (lanes 1 and 7) or stimulated with 50 μM glutamate (15-min pulse) in the absence (lines 2 and 8) or presence (lanes 3 to 6 and 9 to 12) of the drugs as indicated. Both drugs inhibited glutamate-induced increase of NF-kB activity in a concentration-dependent manner (Fig.4), with calculated EC_{50} values of 1.3 mM and 6 mM for ASA and NaSal respectively. Parallel experiments in which cell viability was measured at later times (24 h), revealed a strict correlation between neuroprotective concentrations of anti-inflammatory drugs and blockade of NF-kB induction (EC_{50} values of 1.5 mM for ASA and 5.8 mM for NaSal). The salicylate effect on NF-kB/Rel proteins was specific. In fact, ASA and NaSal failed to modify the glutamate-mediated nuclear induction of the transcriptional complex AP-1 (Fig. 4).

Therefore it is ascertained that, at concentrations compatible with plasma levels reached during treatment of chronic inflammatory states, salicylates prevent glutamate-induced neurotoxicity.

Interestingly, the site of action common to ASA and NaSal, but not to indomethacin, is the blockade of induction of NF-kB transcription nuclear factors, which is a indisputable prove of the relationship between neuroprotection and cellular event.

The results were obtained preparing primary cultures of cerebellar granule cells from cerebella of 8-day-old rats (Sprague-Dawley). The cultures were used at 10-12 days in vitro (DIV), and contained > 95% glutamatergic granule neurons. Neurotoxicity was induced essentially as follows: cells were washed twice with Mg^{2+}-free Locke solution [154 mM NaCl; 5.6 mM KCl; 3.6 mM $NaHCO_3$; 2.3 mM $CaCl_2$; 5.6 mM glucose; 5 mM HEPES (buffer solution base on N-[2-hydroxyethyl]-piperazin-N'-ethanesulfonic acid) free from magnesium ions and afterwards were incubated with 50 µM glutamate in Locke solution free from magnesium ions for 15 minutes (25°C). The glutamate-containing solution was then removed by aspiration and the cells were washed twice with Locke solution containing 1 mM Mg_2SO_4, then returned to the incubator in their original medium. Cell survival was evaluated after 24 hours, according to the procedure by K.H. Johnes et al. J. Histochem, Cytochem. 33, 77 (1985).

Hippocampal slices were obtained from eight-day old Sprague-Dawley rats. Sections were prepared according to what described by J. Gathwaite et al., Neurosci. Lett. 97, 316 (1989). Transverse slices of hippocampus cut at

a thickness of 0.5 mm by a Vibroslice (Campden Instruments LTD, U.K.), were submerged in 2 ml of a Krebs solution containing 11 mM glucose, equilibrated with 95% O_2 - 5% CO_2 (pH 7.4), and preincubated at 37°C for 30 min. After that, 30 µm NMDA was added and incubation was carried out for 30 min. At the end of this period, slices were washed and further incubated in fresh buffer for 90 min in order to allow irreversibly damaged neurons to become visibly necrotic while giving reversibly damaged cells time to recover. Test drugs, ASA and NaSal, were added to slices since the preincubation period. Slices were fixed in a mixture of 4 % paraformaldehyde and 2.5 % glutaraldehyde in 0.1 M phosphate buffer (pH 7.4) then embedded in epoxy resin consisting of glycid ether; 2-dodecenylsuccinic anhydride; methylnadic anhydride; 2,4,6-tris-(dimethylaminomethyl)phenol; respectively in the following ratios 6 : 3 : 3.5 : 0.25 by volume. Semithin sections were cut in the plane of the hippocampal slices, stained with methylene blue and azur II and examined under light microscopy.

To perform a quantitation of cell loss, adjacent cells were counted in cell layer fields taken from CA1, CA3 and the dorsal blade of dentate gyrus. The considered fields measured 1.5×10^4 mm^2. The percentage of cell survival was calculated by the ratio of living cells to total cell number.

It has therefore been proved that non-steroidal antiinflammatory compounds according to the invention have an unexpected capability of effectively counteracting neurodegenerative conditions, by acting directly at the level of neuronal cells.

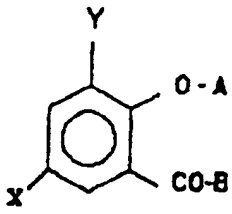
It should be noted, with respect to those compounds of the invention defined at point (a), that such a characteristic makes their pharmacological spectrum wider than that of other NSAIDs.

Therefore, it is unexpectedly possible to use the compounds of the invention previously defined at point (a) also in patients affected with neurodegenerative diseases associated with glutamate-mediated neuronal damages but not with inflammatory conditions, since said compounds have such double and distinct capability of acting as both antiinflammatory and antidegenerative agents.

CLAIMS

1. The use of non-steroidal antiinflammatory compounds selected from:

(a) the group of compounds deriving from acetylsalicylic acid of the following formula (I)



(I)

wherein:

A is H; (C_1-C_4)-alkyl, optionally substituted with a carboxyl group; (C_3-C_4)-alkenyl or alkynyl; phenyl optionally substituted with a carboxyl group; naphthyl; COR, SO_3R;

B is OR^1; NHR^2;

R is (C_1-C_4)-alkyl;

R^1 is H; an ammonium cation; a pharmaceutically acceptable cation of an alkali or alkaline-earth metal or of an organic base; (C_1C_4)-alkyl, optionally substituted with a hydroxyl or phenoxyl group, which can in its turn optionally be substituted with an acetamino group; phenoxyl optionally substituted with an acetamino group;

R2 is H; (C_2-C_4)-alkanoyl;

X is OH; NH_2; phenyl optionally substituted with one or more fluorine atoms; 4,5dihydro-2-phenyl-3H-benzindol-3-yl; p-aminobenzenesulfonamido; 4-[(pyridinylamino)sulfonyl]phenyl-;

Y is H; OH;

and the pharmaceutically acceptable salts and metabolites thereof;

(b) the group of compounds with antiinflammatory acitivity consisting of tolmetin, ketorolac, diclofenac, ibuprofene, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, piroxicam, tenoxicam, meloxicam, nabumetone, aminopyrine, apazone, phenylbutazone, oxyphenbutazone, antipyrine, nimesulide, sulindac, etodolac, sodium meclofenamate, zileuton;

and the pharmaceutically acceptable salts and metabolites thereof;

(c) benzoic acid, 2,3-dihydroxy-benzoic acid and sulfanylamide;

and the pharmaceutically acceptable salts and metabolites thereof;

for the preparation of a medicament for the prevention and/or the treatment of glutamate receptor-mediated neuronal damages.

2. The use as claimed in claim 1, wherein said compounds defined sub (a) are selected from the group consisting of: acetylsalicylic acid, sodium salicylate, salicylamide, salicylamide- Oacetic acid, salacetamide, flufenisal, diflunisal, acetaminosalol, calcium acetyl-salicylate, benorylate, fendosal, salicyl-sulforic acid, etersalate, gentisic acid, glycol salicylate, mesalamine, imidazole salicylate, lysine acetylsalicylate, morpholine salicylate, 1-naphthyl salicylate, parsalmide, phenyl acetylsalicylate, salsalate, sulfasalazine, olsalazine, methyl salicylate, methyl acetylsalicylate.

3. The use as claimed in claim 1 or 2, wherein said drugs are acetylsalicylic acid and sodium salicylate.

4. The use as claimed in claims 1 to 3, for the preparation of a medicament for the prevention and/or the treatment of Alzheimer's disease, amyotrophic lateral sclerosis, cranial and spinal traumas, multi-infarct dementia, Lewy Body dementia, AIDS-associated dementia, central and peripheral ischemic neuropathies, neuropathies due to anoxic and/or glycemic damages, multiple sclerosis, infective and/or toxic neurodegenerative diseases, neurodegenerative syndromes in prion diseases, ataxias-telangiectasias, epilepsy-related neurodegenerative processes, metabolic neuropathies and other related neuropathologies.

5. The use as claimed in claims 1 to 3, for the preparation of a medicament for the prevention and/or the treatment of Parkinson's disease.

6. The use as claimed in claims 1 to 3, for the preparation of a medicament for the prevention and/or the treatment of Huntington's disease.

7. A method for the prevention and the treatment of glutamate receptor-mediated neuronal damages in a patient, which method comprises administering said patient with an effective amount of a selected non-steroidal antiinflammatory compound as defined in claim 1.

A

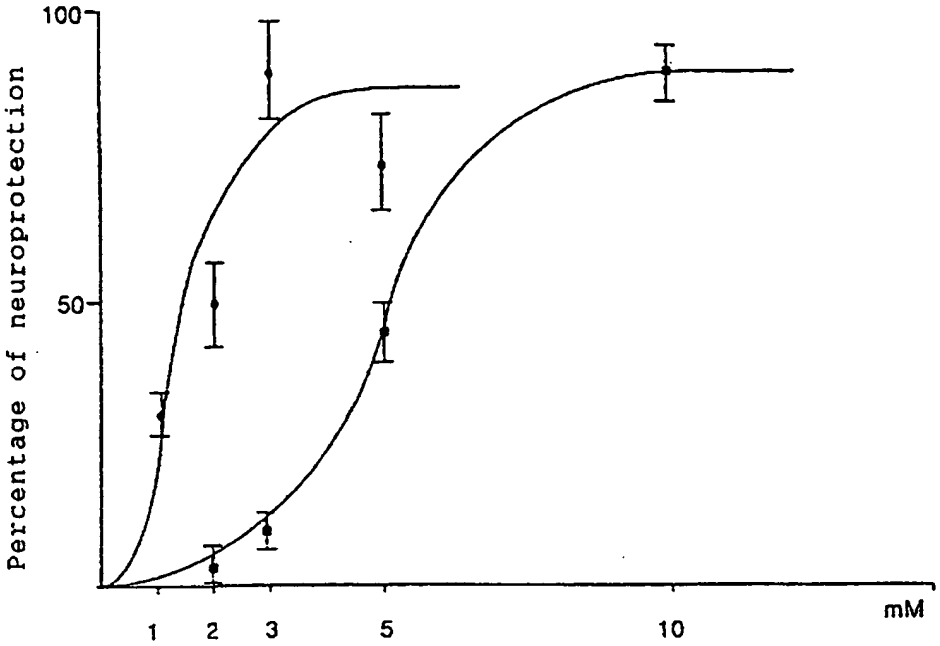


FIG. 1

C

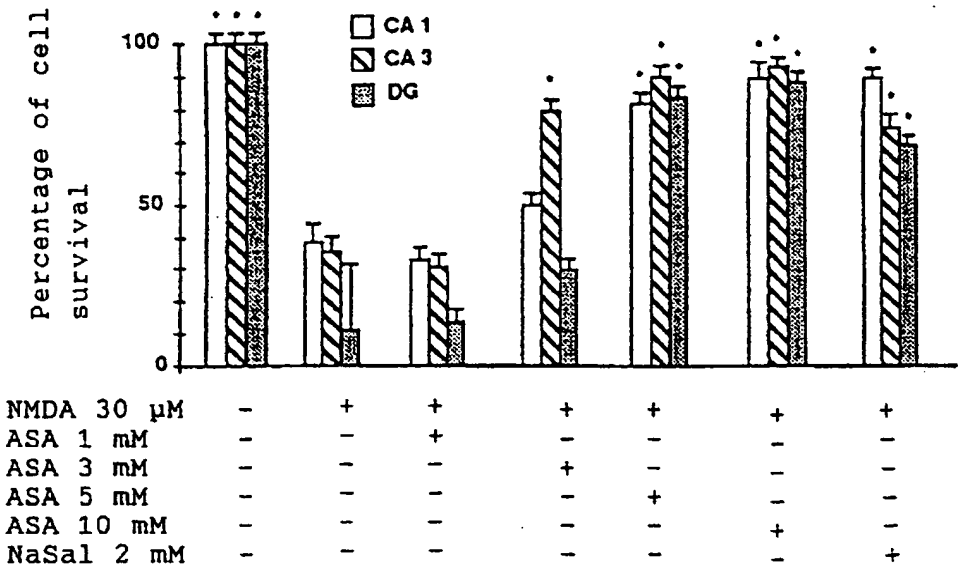

Percentage of cell survival
100
50
0
CA 1
CA 3
DG
NMDA 30 µM - + + + + + +
ASA 1 mM - - + - - - -
ASA 3 mM - - - + - - -
ASA 5 mM - - - - + - -
ASA 10 mM - - - - - + -
NaSal 2 mM - - - - - - +

FIG. 2

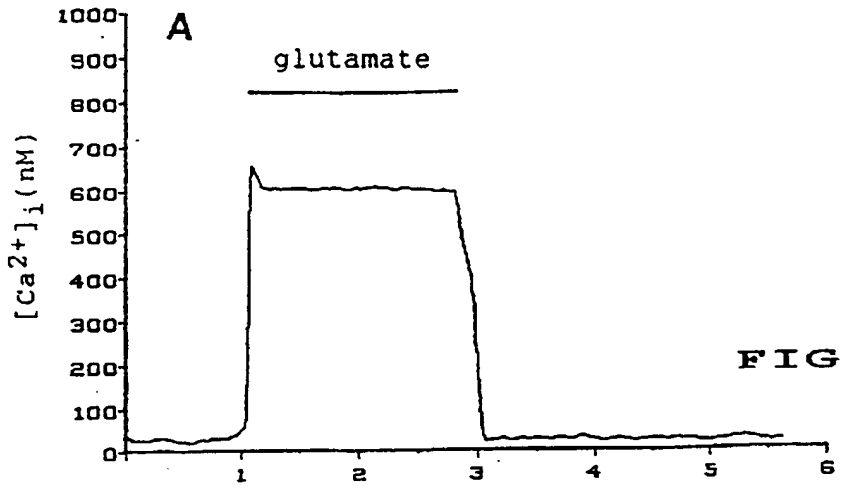

A
glutamate
$[Ca^{2+}]_i$(nM)
1000
900
800
700
600
500
400
300
200
100
0
1
2
3
4
5
6

FIG. 3A

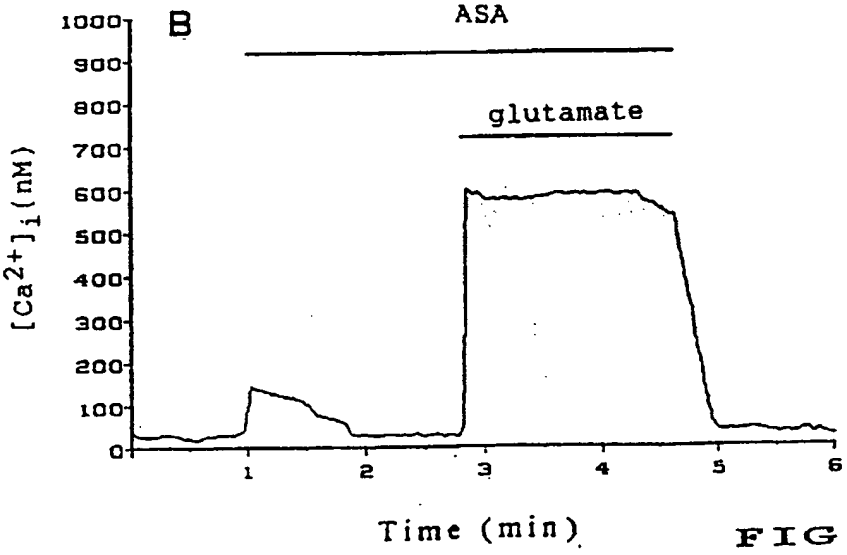

B
ASA
glutamate
$[Ca^{2+}]_i$(nM)
1000
900
800
700
600
500
400
300
200
100
0
1
2
3
4
5
6
Time (min)

FIG. 3B

FIG. 4